Clinical versus Echocardiographic Parameters in Assessing Cardiac Resynchronisation Therapy Response in a Multiethnic Asian Population

Dear Editor,

Systolic heart failure is the most common cardiac cause for admission to Singapore hospitals, accounting for approximately 25% of such hospital stays.[1] Age-adjusted heart failure admission rates rose 40% over 7 years from 1991 to 1998.[2]

Studies have shown that cardiac resynchronisation therapy (CRT) not only reduced recurrent hospitalisation rate in selected symptomatic patients with systolic heart failure,[3,4] but more importantly, resulted in up to 35% of relative risk reduction in mortality.[3,5]

However, the correlation between improvements in clinical response based on the New York Heart Association (NYHA) system of heart failure versus echocardiographic parameters remained uncertain. Bleeker et al[6] observed a discrepancy between clinical response and echocardiographic response: only 51% of CRT patients with improvement in NYHA class showed reductions of >15% in left ventricular end systolic volume (LVESV). Most of the studies, however, involved predominantly non-Asian population.

The objective of this study was to evaluate the correlation between clinical response rates versus echocardiographic end points in CRT patients in our institution.

Materials and Methods

We conducted a retrospective study in our centre from 2009 to 2014 by recruiting all CRT patients with follow-up of at least 6 months. All had transthoracic echocardiography and documentation of NYHA status pre- and post-CRT implantation.

Based on previous studies,[6,7] CRT responders were defined as either "clinical improvement of ≥1 NYHA class (clinical responder)" or "improvement in echocardiography parameters (echocardiographic responder)". Echocardiographic responders were defined as either "an absolute improvement in left ventricular ejection fraction (LVEF) >5% (measured by Simpson's Biplane method)", and/or "a reduction in LVESV of >15% on transthoracic echocardiography (non-contrast method in evaluating LVEF and LV volumes) using either General Electric or Philips echo machines, at least 6 months following CRT device implantation".

Data was expressed as mean ± standard deviation for continuous variables and as frequency and percentages for discrete variables. Continuous variables were compared using independent sample t-tests. Categorical variables were compared using chi-squared tests. Statistical agreement among NYHA class and echocardiographic parameters were performed using Cohen κ-coefficient. The κ-coefficient ranges from -1 (perfect disagreement) to +1 (perfect agreement) whereas κ-coefficient of 0 indicates that the amount of agreement was exactly expected by chance. For all tests, a P value of <0.05 was considered statistically significant.

This study was reviewed and approved by the hospital institutional review board.

Results

A total of 32 patients received CRT during the study period. However, only 24 patients were included in the study as 4 patients had follow-up duration of less than 12 months and the remaining did not have post-CRT transthoracic echocardiography evaluation. The baseline characteristics of the study population are shown in Table 1. Majority were male (79.2%) and Chinese (62.5%). Ischaemic cardiomyopathy (66.7%) was the most common cause of cardiomyopathy. Mean follow-up duration was 26.9 ± 16.9 months.

Prior to CRT implantation, 45.8% were in NYHA class III and IV while 45.8% of subjects had left bundle branch block morphology. QRS duration was 156 ± 16 milliseconds. Mean duration of transthoracic echocardiography performed post-CRT device implantation was 16 months.

Overall, compared with pre-CRT, there was significant improvement in NYHA class (P = 0.008), LVEF (pre-CRT: 24.6 ± 7.9%; post-CRT: 35.5 ± 11.2%; P = 0.001) and LVESV (pre-CRT: 114.1 ± 50.1 mL; post-CRT: 83.6 ± 43.4 mL; P = 0.017) post-CRT (Table 2). Responder rate was highest for NYHA class (83.3%), followed by LVEF (62.5%) and lowest for LVESV at 54.2%.

Despite 66.7% of patients showing improvement in both NYHA class (clinical responder) and echocardiography parameters (either improvement in LVESV and/or LVEF), there was poor κ-coefficient agreement between

Table 1. Baseline Characteristics

Characteristic	Value
Age at implant (years), mean ± SD	60 ± 8
Male (%)	79.2
Ethnicity (%)	
Chinese	62.5
Malay	25.0
Indian	8.3
Others	4.2
Comorbidities (%)	
Diabetes	54.2
Hypertension	50.0
Atrial fibrillation	25.0
Cardiomyopathy (%)	
ICMP	66.7
NICMP	33.3
QRS complex	
Left bundle branch block	45.8
Right bundle branch block	20.8
Complete heart block	33.4
QRS duration (millisecond) prior CRT, (mean ± SD)	156 ± 16
Medications, %	
Beta-blocker	95.8
ACE inhibitor/ARB	70.8
Diuretics	87.5
Potassium-sparing diuretics	58.3
Statin	83.3
Aspirin	62.5

ACE: Angiotensin-converting-enzyme; ARB: Angiotensin II receptor blockers; CRT: Cardiac resynchronisation therapy; ICMP: Ischaemic cardiomyopathy; NICMP: Non-ischaemic cardiomyopathy; SD: Standard deviation

Table 2. NYHA Class, LVEF and LVESV Before and After CRT Implantation

	Before CRT	After CRT	*P* Value
NYHA (%)			
Class I	12.5	58.3	
Class II	41.7	29.2	
Class III	45.8	12.5	
Class IV	0	0	0.008
LVEF (%)	24.6 ± 7.9	35.5 ± 11.2	0.001
LVESV (mL)	114.1 ± 50.1	83.6 ± 43.4	0.017

NYHA: New York Heart Association; CRT: Cardiac resynchronisation therapy; LVEF: Left ventricular ejection fraction; LVESV: Left ventricular end-systolic volume

Table 3. Agreement between Clinical Responder and Reduction in LVESV >15%

	Clinical Responder	Clinical Non-Responder
LVESV reduced >15%	12 (50.0%)	1 (4.2%)
LVESV reduced ≤15%	8 (33.3%)	3 (12.5%)

LVESV: Left ventricular end-systolic volume

Table 4. Agreement between Clinical Responder and Improvement in LVEF >5%

	Clinical Responder	Clinical Non-Responder
LVEF improved >5%	14 (58.3%)	1 (4.2%)
LVEF improved ≤5%	6 (25.0%)	3 (12.5%)

LVEF: Left ventricular ejection fraction

NYHA and LVESV, κ = 0.21 ± 0.16 (Table 3) as well as NYHA class and LVEF, k = 0.30 ± 0.19 (Table 4). About 25% showed either a positive clinical response or echocardiographic response while the remaining 8.3% were non-responders (no improvement in NYHA class as well as both echocardiography parameters) (Fig. 1). The disagreement was mainly caused by patients who showed improvement in clinical response without improvement in LVESV, 33.3% (Table 3) or LVEF, 25% (Table 4). The κ-coefficient between LVEF versus LVESV post-CRT was poor as well, κ = -0.32 ± 0.20.

Patients with non-ischaemic cardiomyopathy had significantly higher echocardiographic response rate, 87.5% (based on LVESV reduction of >15%) compared to patients with ischaemic cardiomyopathy (ICMP), 37.5% (*P* = 0.02).

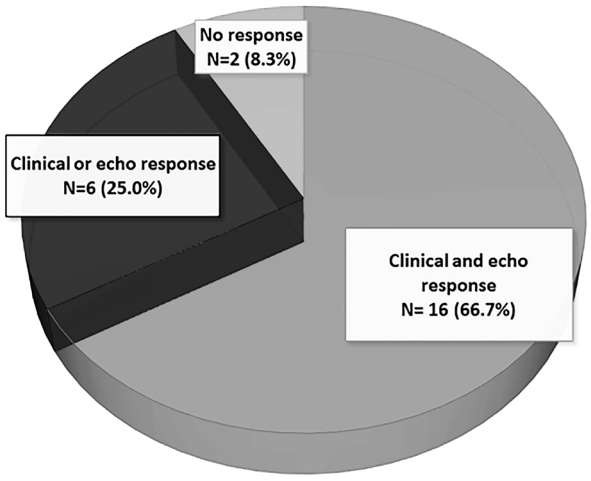

Fig. 1. Pie chart showing the clinical versus echocardiographic parameters (LVEF and/or LVESV) to assess response to CRT. CRT: Cardiac resynchronisation therapy, LVEF: Left ventricular ejection fraction, LVESV: Left ventricular end-systolic volume

Discussion

Previous studies[7-11] have reported different rates of response to CRT when different definitions of response (up to 17 response parameters) were used. The parameters (NYHA class, LVEF and LVESV) that were used in this retrospective study were the most widely accepted parameters.[7] This study showed that in a multiethnic Asian population, up to 83.3% of patients responded to CRT using NYHA class assessment (clinical responder). However, the responder rate based on echocardiographic parameters (LVEF responder rate: 62.5%; LVESV responder rate: 54.2%) were lower when compared to NYHA class. These findings were consistent with previous studies.[6,8,11,12]

Even though up to 66.7% of patients showed improvement in both NYHA class (clinical responder) and echocardiography parameters (either improvement in LVESV and/or LVEF), the κ-coefficient agreements were poor between NYHA class and LVESV ($\kappa = 0.21 \pm 0.16$ [Table 3]), as well as NYHA class and LVEF ($k = 0.30 \pm 0.19$ [Table 4]). The disagreement was mainly caused by patients who showed clinical responses without either improvement in LVEF (25.0%) or LVESV (33.3%). This observation may be explained by the presence of multifactorial effects including an improvement in efficiency as well as oxygen utilisation which may not be fully reflected in echocardiographic measurements of cardiac function. The κ-coefficient between LVEF versus LVESV was poor as well ($\kappa = -0.32 \pm 0.20$), although it appears consistent that half to two-thirds of cohort are echocardiographic responders by either echocardiographic parameters. This suggests that these 2 echocardiographic parameters may be assessing different aspects of cardiac function and may also represent different stages of left ventricular remodelling. These echo parameters could also be confounded by measurement and interobserver variability. LVESV may be a more sensitive and reproducible marker of response than LVEF which may have greater measurement variability. Furthermore, the mechanism of clinical improvement may not be entirely mediated by improvement in LVEF and/or LVESV. Perhaps more standardised and specific parameters, such as peak oxygen consumption at exercise (Vo_2max), should be used in assessing response to CRT that could accurately predict outcomes.

The main limitation of our study was a retrospective single centre study with a small number of subjects. As this was a retrospective study, the interobserver agreement was not evaluated for LVEF and LVESV measurements. Furthermore, studies[13] have shown that the 2-dimensional echocardiographic evaluation of LVEF and LV volumes was found to be more accurate when adding an intravenous contrast agent. Besides, although NYHA class improvement and the selected echo parameters are established methods of determining CRT response, they could potentially overestimate the true response rate as neither subjects nor doctors were blinded to the presence of the CRT. Our study population was relatively heterogeneous; in particular, we included patients with atrial fibrillation, right bundle branch block as well as complete heart block. Our study follow-up was relatively short (mean follow-up duration was 26.9 ± 16.9 months) as CRT has been shown to have persistent, increasing benefits with a longer mean follow-up of 56 months.[14,15]

Conclusion

Our local data showed CRT-responder rate of 66.7% (improvement in both clinical and echocardiographic parameters) as well as discordance between clinical versus echocardiographic response. These findings were similar to previous established publications mainly involving Caucasian population.

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